IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/016,850 Confirmation No. 7435
Applicant : HUGHES et al.
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Title : PHARMACEUTICAL CONJUGATES WITH ENHANCED PHARMACOKINETIC CHARACTERISTICS

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DECLARATION OF PATRICK HUGHES Ph.D. (37 CFR § 1.132)

Dear Sir,

I, Patrick Hughes, Ph.D., am an inventor of the subject matter claimed in United States Patent Application Serial No: 10/016,850, and I hereby make the following declaration.

1. I received a Bachelor of Science degree in Pharmacy from the St. Louis College of Pharmacy in 1989. I was awarded a Ph.D. from Purdue University in 1995, by the School of Pharmacy and Pharmaceutical Sciences. My research project concerned the transcorneal ocular delivery of acycloguanosine analogues and evaluation of

the compounds both in vitro and in vivo using a rabbit model.

2. From 1989 to 1991 I was a teaching assistant (Clinical Pharmacokinetics) in the School of Pharmacy and Pharmaceutical Sciences, Purdue University. From 1989 to 1995 I was a Graduate Research Assistant in the School of Pharmacy and Pharmaceutical Sciences, Purdue University, where I did extensive development of analytical methods using High Performance Liquid Chromotography to study drug metabolism, and developed animal models for the study of ocular delivery of drugs.

3. I have received numerous awards and fellowships for my studies in drug delivery. Additionally, I am an author of a number of scientific papers concerning ocular drug delivery. Most recently I have co-edited an edition of Advanced Drug Delivery Reviews "Drug Delivery Strategies to Treat Age-Related Macular Degeneration", P. M. Hughes and O. Olejnik eds. Volume 57, Issues 14, 13 December 2005.

4. From 1995 to present I have been employed at Allergan, Inc. I have been responsible for predevelopment, formulation development and preformulation. In these roles I have served as CMC Team leader and Global Project Team leader for several drug delivery projects. I am currently Director of Preformulation and will take over the role of Director, Early Development in January 2007.

5. I understand that the present patent application has been rejected as allegedly unpatentable under 35 U.S.C.

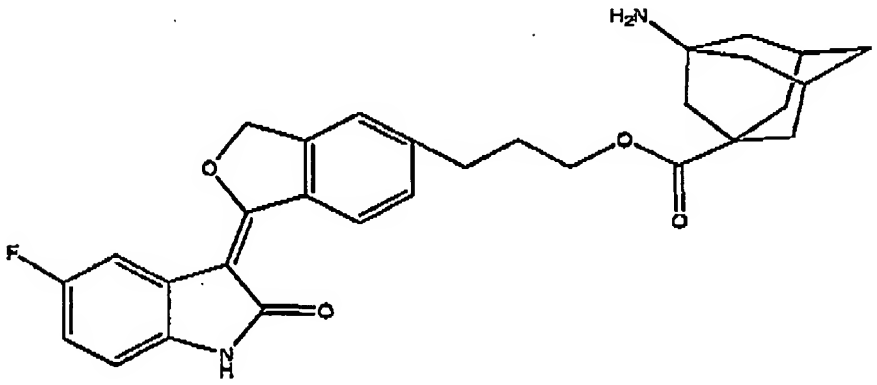
§103(a) over the combination of DeSantis (U.S. Patent Publication 2001/0047012), which discusses the combined topical use of a glutamate antagonist and an intraocular pressure (IOP) lowering agent for the treatment of glaucoma and ocular hypertension and Collins et al., (WO 01/92288), which discloses the use of antibiotic/vitamin B12 conjugate for targeted therapy and imaging of infections.

6. The combined topical use of a glutamate antagonist and an intraocular pressure (IOP) lowering agent disclosed by DeSantis requires that the IOP lowering agent is substantially localized in the anterior chamber of the eye, wherein it may exert its ocular hypotensive activity, thus helping prevent mechanical "crushing" ischemic damage to the retina caused by high IOP.

7. The present invention comprises an ophthalmic composition containing a conjugate that includes an admantane-based targeting moiety and a therapeutic component. The targeting moiety directs the therapeutic component to the retinal epithelium (located in the posterior rather than the anterior segment of the eye), as demonstrated in the following experiment.

8. In the eye, melanin is found in the cells of the retinal epithelium located in the posterior segment of the eye and in the iris. The conjugates of the present invention will preferentially deliver the therapeutic agent to the posterior segment in an amount at least several fold that delivered to the anterior segment. To show the selective binding of these conjugates to

melanin, the following compound (a tyrosine kinase inhibitor bound to adamantaneamine), designated Compound A and comprising an embodiment of the claimed compositions in the present patent application, was synthesized:



9. A melanin binding study was conducted using Compound A. Concentrations of Compound A ranging from 5 µM to 40 µM were incubated with 1 mg/ml of melanin in deionized water. After 15 minutes incubation, Compound A was almost entirely bound to the melanin after 15 minutes at all tested concentrations, indicating that saturation of the melanin by the prodrug had not been reached. The data are shown in Table 1, shown below. The binding of the adamantineamine moiety of the conjugate to melanin was rapid, reaching equilibrium within an incubation time of 15 minutes.

Table 1. Bound Concentrations of Compound A in 1 mg/ mL Sepia Melanin

Compound A Conc. (μM)	Compound A Free (μM)	Compound A Bound (μM/mg)
4.98	1.42	3.56
9.95	1.42	8.53
19.90	1.47	18.43
29.85	1.61	28.24
59.69	1.65	58.04

10. Another experiment used a lower concentration of melanin in an attempt to determine saturation concentrations of Compound A, in vitro. Under similar conditions as in the previously described experiment, 0.02 mg/ml of melanin was incubated with Compound A at concentrations ranging from 10 to 40 μM. Again, the amount of Compound A bound to the melanin was a function of the amount added to the incubation mixture at all concentrations, thus indicating that saturation had not yet occurred. The data is shown in Table 2.

Table 2. Bound Concentrations of Compound A in 0.02 mg/ mL Sepia Melanin

Compound A Conc. (μM)	Compound A Bound (μM/mg)
10.25	9.01
20.5	15.9
30.74	23.25

40.99	30.48

11. Therefore, these experiments show that the compounds of the present invention have the ability to quickly and selectively bind melanin, a compound found in high concentrations in the retinal-pigmented epithelial (RPE) cells located in the posterior segment of the eye. Because of this selective binding capacity, this experiment thus shows that the prodrugs of the present invention have the ability to target the RPE cells of the posterior segment of the eye, and thereby direct the therapeutic component portion of the product to the posterior segment.

12. Thus, in the event that an embodiment of the conjugates of the present invention were to comprise a conjugate of DeSantis' a glutamate antagonist and IOP lowering agent, the IOP lowering activity of the latter agent would be expected to be compromised by virtue of its targeting to the posterior segment. For this reason, DeSantis addresses a materially different problem and solution than the present invention, which the person of ordinary skill in the art would not expect to work, nor in my opinion would it work, in the manner described by DeSantis for the treatment of ocular hypertension and glaucoma.

13. Collins merely discloses conjugates comprising antibiotics and a targeting moiety that directs the antibiotic to infected tissue. Unlike the presently claimed prodrugs, the conjugates of Collins would not

preferentially direct therapeutic components to the retinal epithelium or the posterior segment of the eye.

14. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the present application or any patent issuing thereon.

Respectfully submitted,

Patrick M. Hughes, Ph.D.

10/13/06

Date